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TOWNSEND AND TOWNSEND AND CREW LLP
TWO EMBARCADERO CENTER
8TH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
FETTEROLF, BRANDON J	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte TAI-TUNG YIP, CHRISTINE YIP, and GEORGE L. WRIGHT, JR.

Appeal 2008-4779
Application 10/088,970
Technology Center 1600

Decided: December 17, 2008

Before ERIC GRIMES, RICHARD M. LEBOVITZ, and MELANIE L. McCOLLUM, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of diagnosing prostate cancer, which the Examiner has rejected as nonenabled. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

"Conventionally, prostate cancer is diagnosed using prostate specific antigen (PSA) as a marker" (Spec. 1: 17-18). However, "many individuals with elevated levels of PSA in the blood serum may not have prostate cancer, but may instead have benign prostate hyperplasia (BPH)" (*id.* at 2: 8-9).

The Specification discloses "methods and kits that can be used as an aid for diagnosis of prostate cancer by measuring markers that are differentially present in samples of a prostate cancer patient and a subject who does not have prostate cancer (*e.g.*, BPH patients)" (*id.* at 2: 19-21). Markers that "are present at an elevated level in samples of prostate cancer patients compared to samples of BPH patients . . . include polypeptides having an apparent molecular weight of about 2776 Da, 4423 Da, 4480 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 7843 Da, 8030 Da, 8240 Da, or 8714 Da" (*id.* at 2: 34 to 3: 3).

Claims 1, 8, 12, 20, and 84-94 are pending and on appeal. The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 1 is representative and reads as follows:

1. A method for diagnosing prostate cancer versus benign prostate hyperplasia, the method comprising:

i. obtaining from a subject a sample containing a plurality of prostrate [sic, prostate] related protein markers having apparent molecular weights below 10,000 Da wherein the sample is selected from the group consisting of prostate tissue, blood, serum, semen, seminal fluid or seminal plasma;

ii. determining by mass spectroscopy a representative pattern of the quantity of a plurality of protein markers in the sample, the protein markers having an apparent molecular weight of less than 10,000 Da;

iii. comparing the pattern of the plurality of protein markers having apparent molecular weight of less than 10,000 Da with an amount of a plurality of protein markers having an apparent molecular weight of less

than 10,000 Da from a control sample where the control sample originates from benign prostate hyperplasia;
and

iv. determining whether the pattern of the sample is a diagnostic amount consistent with a diagnosis of prostate cancer versus benign prostate hyperplasia where the pattern consistent with a diagnosis of prostate cancer is represented by an increase in the quantity of lower molecular weight proteins.

ENABLEMENT

The Issue

The Examiner has rejected claims 1, 8, 12, 20, and 84-94 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner's position is that the Specification is enabling for a method of diagnosing prostate cancer by detecting markers of specific molecular weights in a sample of seminal plasma, but is not enabling for diagnosing prostate cancer using any sample and any markers having a molecular weight below 10,000 Da (Answer 3).

Appellants contend that the Specification's disclosure is broader than the use of specific markers in a specific sample, and that the inventors discovered that prostate cancer patients "have an abundance of protease activity" resulting in "a shift in the proteins below a molecular weight of 10,000 Da towards lower molecular weight proteins" (Appeal Br. 6). "The detected masses differ according to the various parameters being applied. What doesn't change is the shifting of the masses below 10,000 Da to lower molecular weights because of increased protease activity in prostate cancer patients compared to those suffering from BPH. This shift in low molecular weight proteins is appellants' invention." (*Id.* at 11.)

The issue to be decided is: Does the evidence of record support the Examiner's conclusion that practicing the claimed method using samples other than seminal plasma, and based on markers other than those identified in the Specification, would require undue experimentation?

Findings of Fact

1. The Specification states that "methods and kits . . . can be used as an aid for diagnosis of prostate cancer by measuring markers that are differentially present in samples of a prostate cancer patient and a subject who does not have prostate cancer (*e.g.*, BPH patients)" (Spec. 2: 19-21).

2. The samples can be "blood, serum, urine, semen, seminal fluid, seminal plasma, or tissue extracts" (*id.* at 3: 15).

3. The Specification states that "'[m]arker' . . . refers to a polypeptide which is differentially present in a sample taken from patients having prostate cancer as compared to a comparable sample taken from subjects who do not have prostate cancer (*e.g.*, benign prostate hyperplasia patients or healthy subjects)" (*id.* at 6: 26-29).

4. The Specification states that "[w]hile the absolute identity of many markers is not yet known, such knowledge is not necessary to measure them in a patient sample, because they are sufficiently characterized by, *e.g.*, mass and by affinity characteristics" (*id.* at 5: 21-23).

5. The Specification provides a working example in which proteins in seminal plasma samples from patients with prostate cancer and BPH were adsorbed to a Ni(II) ProteinChip® array and analyzed by mass spectrometry (*id.* at 31: 12-23).

6. The Specification states that the results showed that "proteins of apparent molecular weight of about 2776 Da, 4423 Da, 4480 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 8030 Da, and 8714 Da were found to be very abundant in a sample from a prostate cancer patient than a sample from a BPH patient" (*id.* at 32: 5-8).

7. The Specification states that the results also showed that "proteins having an apparent molecular weight of about 2276 Da, 2905 Da, 3038 Da, 3600 Da, 3835 Da, 3933 Da, and 4175 Da were found to be very abundant in a sample from the BPH patient than a sample from the prostate cancer patient" (*id.* at 32: 10-12).

8. The Specification states that the binding of these proteins to the Ni(II) ProteinChip® array shows that "these markers can have amino acid[ ] residues, such as histidine, capable of binding to metal ions" (*id.* at 13: 32-33).

9. The Specification provides a second working example, in which proteins in seminal plasma samples from patients with prostate cancer and BPH were adsorbed to an H4 ProteinChip® array and analyzed by mass spectrometry (*id.* at 32: 23-32).

10. The Specification states that the results of this experiment showed that "proteins having an apparent molecular weight of about 2776 Da, 5753 Da, 6098 Da, 6270 Da, 6998 Da, 7843 Da, 8030 Da, and 8240 Da were found to be very abundant in the sample from the prostate cancer patient than the sample from the BPH patient" (*id.* at 33: 11-14).

11. The Specification states that the results of the second example also showed that

> a number of proteins were found to be very abundant in the sample from the BPH patient than in the sample from the prostate cancer patient. For example, proteins having an apparent molecular weight of about 2276 Da, 2530 Da, 2905 Da, 3030 Da, 3224 Da, 3600 Da, and 3915 Da were found to be very abundant in the sample from the prostate cancer [sic, BPH] patient than the sample from the BPH [sic, prostate cancer] patient.

(*Id.* at 33: 17-21.)

12. The Specification states that the binding of these proteins to the H4 ProteinChip® array shows that "these markers can have amino acid residues comprising hydrophobic moieties" (*id.* at 14: 6).

13. The Specification provides a third working example, in which proteins in seminal plasma samples from patients with prostate cancer and BPH were adsorbed to an SCX1 ProteinChip® array and analyzed by mass spectrometry (*id.* at 33: 33 to 34: 8).

14. The Specification states that the results of this experiment showed that "a protein having apparent molecular weight of about 5753 Da was present at a high level (relative intensity of about 52) in the sample of the prostate cancer patient," but present in only a negligible amount in the BPH sample (*id.* at 34: 15-17).

15. The Specification states that prostate specific antigen (PSA) is "a protease with serine protease activity. . . . Its natural substrates are semenogelin I, semenogelin II and fibronectin in the seminal plasma." (*Id.* at 1: 19-22.)

16. The Specification states that "PSA leaks into the blood stream, and measurements of the concentration of PSA in the blood serum have now

found widespread use in detecting prostate cancer in people" (*id.* at 1: 27-29).

17. The Specification does not disclose the substrate(s) of PSA in any sample other than seminal plasma (e.g., blood, serum, urine, or tissue extracts).

18. The Specification states that the protein marker "having an apparent molecular weight of 5753 Da . . . was identified to be seminal basic protein, which is a proteolytic fragment generated by PSA-mediated proteolysis of semenogelin I" (*id.* at 34: 18-22).

19. The Specification states that

> [s]eminal basic protein is abundant in the seminal plasma taken from prostate cancer patients. However, its presence is almost negligible in the seminal plasma taken from BPH patients. This indicates that the PSA in the seminal plasma of a prostate cancer patient is much more active than that in a patient with BPH, since the amount of seminal basic protein present in a sample can reflect the proteolytic activity of PSA.

(*Id.* at 14: 28-32.)

20. The Specification does not identify any protein markers in any sample other than seminal plasma that are diagnostic of prostate cancer or BPH.

21. Appellants have submitted a declaration under 37 C.F.R. § 1.132 by Tai-Tung Yip (received June 26, 2006).

22. The Yip declaration relies on data provided by Adam[1] and Cazares.[2]

23. Adam discloses that proteins in blood samples from patients with prostate cancer (PCA) or BPH, and from healthy men, were quantified by surface enhanced laser desorption/ionization mass spectrometry (Adam, abstract). The results were analyzed by "an artificial intelligence learning algorithm to differentiate PCA from noncancer cohorts" (*id.*)

24. Adam discloses that the "classification algorithm used nine masses between 4 and 10 kDa (4475, 5074, 5382, 7024, 7820, 8141, 9149, 9507, and 9656 Da) to generate 10 terminal nodes" (*id.* at 3611).

25. Each of the 10 terminal nodes corresponds to a conclusion that the set of markers present is diagnostic of PCA, BPH, or normal (*id.*, Fig. 2A).

26. The markers used by Adam all have different molecular weights from the markers disclosed in the present Specification.

27. Cazares discloses that proteins in epithelial cells from tissue samples of patients with prostate cancer, prostate intraepithelial neoplasia (PIN), and BPH were quantified using surface enhanced laser desorption/ ionization mass spectrometry (Cazares, abstract).

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[1] Adam et al., *Serum Protein Fingerprinting Coupled with a Pattern-matching Algorithm Distinguishes Prostate Cancer from Benign Prostate Hyperplasia and Healthy Men*, 62 CANCER RESEARCH 3609-3614 (2002).
[2] Cazares et al., *Normal, Benign, Preneoplastic, and Malignant Prostate Cells Have Distinct Protein Expression Profiles Resolved by Surface Enhanced Laser Desorption/Ionization Mass Spectrometry*, 8 CLINICAL CANCER RESEARCH 2541-2552 (2002).

28. Cazares discloses that "[t]hree peaks (4036, 4361, and 4749 Da) were overexpressed in PIN and PCA with the highest level of abundance in PCA" samples (*id.* at 2544).

29. Cazares discloses that "two peaks (4639 and 2418 Da) were specific to PCA cell lysates but were seen in only 43% of PCA samples tested" (*id.* at 2546, left-hand col.).

30. Cazares discloses that a 5666 Da marker was overexpressed in BPH samples (*id.* at 2546, right-hand col.).

31. Cazares discloses that "the seven most significant differentially expressed peaks," or markers, had molecular weights of 4036, 4361, 4413, 4639, 4729 [sic, 4749?], 5666, and 28,422 Da (*id.* at 2547, left-hand col.).

32. The markers used by Cazares all have different molecular weights from the markers disclosed in the present Specification.

33. The markers used by Cazares all have different molecular weights from the markers used by Adam.

34. Dr. Yip declares that the Adam and Cazares papers provide evidence that the results shown in the Specification are reproducible over a larger patient population (Yip declaration, ¶ 6) and that the invention is applicable to samples other than seminal plasma (*id.* at ¶ 7).

Principles of Law

"The enablement requirement ensures that the public knowledge is enriched by the patent specification to a degree at least commensurate with the scope of the claims. The scope of the claims must be less than or equal to the scope of the enablement." *National Recovery Technols., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1195-96 (Fed. Cir. 1999).

"The scope of enablement, in turn, is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation." *Id.* at 1196.

> [T]here must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility.

In re Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991) (footnote omitted).

"While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." *Id.*

Analysis

The Specification discloses that certain, specific proteins (or markers) are found at higher levels in the seminal plasma of patients with prostate cancer as compared to patients with BPH. The Specification also discloses that other markers are found at higher levels in the seminal plasma of patients with BPH as compared to patients with prostate cancer. The Specification makes clear that it is the presence of *specific* markers, identified by molecular weight and binding affinity (e.g., metal binding or hydrophobicity), that is diagnostic of prostate cancer or BPH. Nowhere does

the Specification state or imply that the presence, generically, of markers having molecular weights below 10,000 Da is itself diagnostic of prostate cancer.

To the contrary, the Specification identifies a group of markers as diagnostic of BPH, rather than prostate cancer, that also have molecular weights below 10,000 Da. With only one exception, in fact, all of the identified BPH-specific markers are smaller than all of the identified prostate cancer-specific markers.

Adam and Cazares provide evidence that the markers that are diagnostic of prostate cancer are different in different samples. The Specification provides no guidance regarding which specific markers found in samples other than seminal plasma would be expected to be diagnostic of prostate cancer.

In essence, the Specification describes a method of identifying markers that are diagnostic of prostate cancer in a single type of sample and invites those skilled in the art to try using that method with other samples to see whether they also contain markers diagnostic of prostate cancer, and, if so, to identify the markers that are diagnostic. This invitation to experiment does not constitute an enabling disclosure with regard to the other samples encompassed by the instant claims. "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. . . . Tossing out the mere germ of an idea does not constitute enabling disclosure." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d at 1366.

Appellants argue, though, that their claims are based on the discovery that prostate cancer patients have increased protease activity (because of increased PSA activity) and the increased proteolysis results in an increase in protein markers having a molecular weight below 10,000 Da. (Appeal Br. 6, 11.)

The evidence of record does not support Appellants' theory. The Specification discloses that the 5753 Da marker that is diagnostic of prostate cancer is generated by PSA-directed cleavage of a larger protein. However, the Specification provides no evidence to support a conclusion that the other disclosed prostate cancer-specific markers result from cleavage of larger proteins.

In fact, the evidence contradicts Appellants' theory. If the prostate-specific markers were the result of proteolytic cleavage of larger proteins found in cancer-free samples, one would expect that the markers that were more prevalent in cancer-free samples would be larger than those that were more prevalent in the prostate cancer samples. Such is not the case, however. All of the BPH-specific markers except one are *smaller* than all of the prostate cancer-specific markers. The evidence therefore does not support Appellants' assertion that there is a "shift[ ] of the masses below 10,000 Da to lower molecular weights because of increased protease activity in prostate cancer patients compared to those suffering from BPH" (Appeal Br. 11).

CONCLUSIONS OF LAW

The evidence of record supports the Examiner's conclusion that practicing the claimed method using samples other than seminal plasma, and

based on markers other than those identified in the Specification, would require undue experimentation.

SUMMARY

We affirm the rejection of claims 1, 8, 12, 20, and 84-94 for lack of enablement.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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TOWNSEND AND TOWNSEND AND CREW LLP
TWO EMBARCADERO CENTER
8TH FLOOR
SAN FRANCISCO CA 94111-3834